Published in final edited form as:

Pediatr Radiol. 2016 October ; 46(11): 1552–1561. doi:10.1007/s00247-016-3641-8.

Software-based PET-MR image coregistration: combined PET/MRI for the rest of us!

Matthew S. Robertson¹, Xinyang Liu¹, William Plishker², George F. Zaki², Pranav K. Vyas¹, Nabile M. Safdar¹, and Raj Shekhar^{1,2}

¹Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Health System, 111 Michigan Ave. NW, Washington, DC 20010, USA

²IGI Technologies, Inc., College Park, MD, USA

Abstract

Background—With the introduction of hybrid positron emission tomography (PET)/MRI, a new imaging option to acquire multimodality images with complementary anatomical and functional information has become available. Compared with hybrid PET/CT, hybrid PET/MRI is capable of providing superior anatomical detail while removing the radiation exposure associated with CT. The early adoption of hybrid PET/MRI, however, has been limited.

Objective—To provide a viable alternative to the hybrid PET/MRI hardware by validating a software-based solution for PET/MR image coregistration.

Materials and methods—A fully automated, graphics processing unit-accelerated 3-dimensional deformable image registration technique was used to align PET (acquired as PET/CT) and MR image pairs of 17 patients (age range: 10 months–21 years, mean: 10 years) who underwent PET/CT and body MRI (chest, abdomen or pelvis), which were performed within a 28-day (mean: 10.5 days) interval. MRI data for most of these cases included single-station post-contrast axial T1-weighted images. Following registration, maximum standardized uptake value (SUV_{max}) values observed in coregistered PET (cPET) and the original PET were compared for 82 volumes of interest. In addition, we calculated the target registration error as a measure of the quality of image coregistration, and evaluated the algorithm's performance in the context of interexpert variability.

Results—The coregistration execution time averaged 97 ± 45 s. The overall relative SUV_{max} difference was 7% between cPET/MRI and PET/CT. The average target registration error was 10.7 ± 6.6 mm, which compared favorably with the typical voxel size (diagonal distance) of 8.0 mm (typical resolution: $0.66 \text{ mm} \times 0.66 \text{ mm} \times 8 \text{ mm}$) for MRI and 6.1 mm (typical resolution: $3.65 \text{ mm} \times 3.65 \text{ mm} \times 3.27 \text{ mm}$) for PET. The variability in landmark identification did not show statistically significant differences between the algorithm and a typical expert.

[✉]Raj Shekhar, rshekhar@childrensnational.org.

Compliance with ethical standards

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest None

Conclusion—We have presented a software-based solution that achieves the many benefits of hybrid PET/MRI scanners without actually needing one. The method proved to be accurate and potentially clinically useful.

Keywords

Children; Deformable image registration; Image coregistration; Image fusion; Positron emission tomography; Positron emission tomography/magnetic resonance imaging

Introduction

Positron emission tomography (PET) provides functional data that is invaluable for assessment of oncological processes in both children and adults. Until 2011, PET imaging had been coupled traditionally with computed tomography (CT), initially as standalone, and more recently as integrated hybrid scanners, to provide correlative anatomical data and attenuation correction maps. While PET/CT provides both excellent anatomical and functional data, it comes at the cost of significant radiation exposure. Oncology patients are particularly at risk for high cumulative lifetime doses given the need for frequent disease monitoring and imaging [1, 2]. Children have increased sensitivity to ionizing radiation, as well as an expectedly longer post exposure lifespan [3–5]. There has been a concerted effort through the Society for Pediatric Radiology and its Image Gently campaign to optimize pediatric imaging protocols toward as low as reasonably achievable (ALARA) principles to mitigate the possible long-term effects of ionizing radiation.

The multimodality of PET/CT imaging allows strategies of minimal radiation to be employed on two fronts: decreasing PET dose and decreasing CT dose. Technical considerations limit the extent to which the PET dose can be modulated. In 2010, North American consensus guidelines provided a reference for recommended weight-based ranges for administered dose [6]. More recently, 2014 consensus guidelines from the Society of Nuclear Medicine and Molecular Imaging and the European Association of Nuclear Medicine established recommended minimum doses of ^{18}F -fluorodeoxyglucose (FDG) for PET imaging [1]. Decreasing CT dose below that of diagnostic quality has been shown as a viable option with the trade-off of decreased anatomical contrast resolution [7–10]. Although the low-dose technique is adequate in high-contrast anatomical regions, such as the lungs and bone, soft-tissue findings can be easily obscured. In these cases, additional imaging such as contrast-enhanced MRI or CT is often needed for follow-up.

With the commercial introduction of hybrid PET/MRI systems beginning in 2011, a new option has become available to provide improved anatomical detail, compared with CT, while decreasing radiation risk exposure. While theoretically offering the best of both worlds, early adoption of hybrid PET/MRI has been limited. The physical footprint, need for both magnetic and radiation shielding, and the physical infrastructure necessary to house the current generation PET/MRI scanners can be daunting for many medical centers, particularly those in urban settings. The capital investment required for initial purchase and infrastructure upgrade, coupled with the lower volume of PET imaging performed in pediatric centers, puts procurement of a new PET/MRI scanner outside the financial capacity

of many pediatric centers that have recently upgraded from PET to PET/CT hybrid scanners in the past decade.

As most academic pediatric centers already have PET/CT and MRI scanners available, we present a solution of using data acquired from existing hardware, coregistered by a software algorithm in a clinically practical minute-order speed, to produce a PET-MR image data set for clinical interpretation. We believe that our solution can provide visually appealing and technically adequate data without significant misregistration or alteration of maximum standardized uptake value (SUV) to serve as a viable alternative to the need for upgrading to the hybrid PET/MRI hardware.

Materials and methods

A retrospective analysis was performed using Montage software (Montage Healthcare Solutions, Inc., Philadelphia, PA, USA) to identify all patients at our hospital who underwent PET/CT and body MRI (chest, abdomen or pelvis) between January 2011 and August 2013. In particular, we focused on patients who underwent low-dose (9 mA–10 mA in our case) attenuation correction (AC)-only CT. Using AC-only CT, indeed, lowers the radiation exposure associated with high-dose (typically 90 mA–250 mA) diagnostic CT. Seventeen patients (age range: 10 months – 21 years, mean: 10 years) meeting the inclusion criteria of having studies performed within a 28-day (mean: 10.5 days) interval were identified. This time frame was selected to minimize the possibility for interval therapeutic intervention (surgery, chemotherapy, etc.). These patients were selected for application of the registration algorithm to the clinical MR and PET/CT images and a new coregistered PET (cPET) data set was created in the DICOM format. In 15 of the 17 cases, MRI data included single-station post-contrast axial T1-weighted images. In the remaining two cases, no post-contrast images were obtained. The MRI data were noncontrast axial images T1-weighted images in one case and noncontrast axial T2-weighted images in the other. Indications for imaging included four patients with neurofibromatosis type-1; three with rhabdomyosarcoma; two with primitive neuroectodermal tumor; two with lymphoma; two with Ewing sarcoma, and one each with spindle cell sarcoma, hepatocellular carcinoma, hepatoblastoma and renal cell carcinoma. Patient data sets were stripped of protected health identifiers and managed in a HIPAA (Health Insurance Portability and Accountability Act)-compliant fashion. For this type of study, formal consent is not required.

Registration algorithm

The deformable registration algorithm is based on previous work [11, 12] and is described briefly here. The multilevel algorithm starts by performing rigid registration between the two volumetric data sets. The downhill simplex method is used for optimization in rigid registration due to its fast, robust convergence properties, particularly in the face of noise, which is common in practical images. On every subsequent level, each volume is divided into eight smaller volumes by dividing along each of the three axes, and independent rigid registration takes places between corresponding subvolumes. By repeating the volume subdivision and registration processes, local displacements due to soft-tissue deformations can be estimated and then turned into a smooth deformation field using quarternion

interpolation. This process of deformable registration is shown schematically in Fig. 1. Constraints within the algorithm ensure physically impossible folding does not occur. Normalized mutual information [13] is used to calculate the intensity-based image similarity between the two corresponding subvolumes. Normalized mutual information from previous levels is factored into the image similarity computation to improve the quality of intensity correlations found at smaller subvolumes. Even with normalized mutual information from previous levels, small subvolumes can be especially susceptible to local noise, so downhill simplex optimization is employed again at this level of the algorithm due to its resilience in the presence of noise. Although fully automatic, a limitation of this and other image similarity-based deformable registration algorithms is the lengthy computation time. To achieve the clinically practical speed of less than a minute, we have accelerated our algorithm in a commercially available graphical processing unit. To our knowledge, our algorithm is the only one to use 6-parameter rigid registration at the local subvolume level to model global nonrigid deformation. The structure of our algorithm lends itself well to high performance mutual information optimization on a graphical processing unit.

Graphical processing unit acceleration

By strategically grouping computation that can execute concurrently with some coordination, a programmer can effectively map an application to cores, shared memory structures and synchronization mechanisms on a graphical processing unit for accelerated computing. In our case, a subvolume of the image is assigned to one group of threads, and a voxel within a subvolume is assigned to a thread, which executes on a single core. Each subvolume is optimized independently of the others, while voxels within a subvolume share memory resources. By mapping effectively to a high-performance graphical processing unit, we achieve orders of magnitude acceleration over baseline central processing unit (CPU) implementations, enabling clinically viable processing times. In our experiments, the graphical processing unit-accelerated registration algorithm written in CUDA (Compute Unified Device Architecture, NVIDIA, Santa Clara, CA, USA) programming framework was run on an independent workstation (Intel® Core™ i7-3820 @ 3.60GHz × 8 CPUs with 32GB random access memory (RAM) and a GeForce GTX 680 GPU, which has 1,536 cores running at 1GHz with 2GB of RAM). The hierarchical subdivision in the registration algorithm continued until the final cubes were 32 voxels on an axial edge. This termination condition meant that the subdivision went on for four levels on the full resolution images used here.

Validation

Our registration algorithm can register MRI to PET or PET to MRI. For the images used in this study, MRI (typical resolution: 0.66 mm×0.66 mm×8 mm) has higher in-plane resolution than PET (typical resolution: 3.65 mm×3.65 mm×3.27 mm), and, because the transformed image is in the space and resolution of the reference image, we register the PET image to the MR image. This produces the highest resolution final fusion image. If we register MR to PET, we expect similar registration accuracy. However, the visualization of the fused image will degrade because of the lower in-plane resolution of PET. Following registration, PET/CT, MR and cPET images were uploaded into an Advantage Workstation Version 4.5 (General Electric, Fairfield, CT, USA) for visual assessment of image alignment

and SUV calculations. Analysis was performed on 16 of the 17 data sets; one MRI data set that was redacted was unable to be loaded into the Advantage Workstation software and thus was excluded from SUV evaluation. Volumes of interest were selected for lung, liver, kidney, bone and muscle, as present on the imaging field of view, and maximum SUV (SUV_{max}) values were calculated. Furthermore, 14 of the 16 patients had neoplastic lesions and additional SUV_{max} values were also calculated for one or two lesions, as present within the coregistered field of view. For each volume of interest, a 2-cm diameter sphere was used as the default volume, with decrease in size as necessary to fit within the tissue of interest, or increase in size to fully encompass all of the selected kidney and proximal ureter for measurement of renal activity.

The accuracy of cPET-MRI registration was evaluated by comparing the spatial correspondence of selected anatomical landmarks (3-D locations in the image space) as given by the algorithm against a reference. A suitable reference is to rely on the correspondence established by clinical experts who identify homologous landmarks in both PET and MR images [14]. Three board-certified radiologists, experienced in interpreting both PET and MR images (M.S.R., fellow, N.M.S. with 9 years' experience, P.K.V. with 20 years' experience), participated in the validation procedure. None of the radiologists involved in the validation process had previously utilized hybrid PET/MR in clinical practice. For each patient, the experts identified and marked the same four preselected anatomical landmarks using 3-D Slicer [15]. Preselected anatomical landmarks varied from case to case depending on the coverage. Example landmarks were renal calices, intervertebral disks and the margin of solid organs. We ensured that the selected landmarks were unambiguously identifiable by the experts on both PET and MR images and believed that the four widely spaced landmarks were sufficient to validate the coregistration method.

To evaluate the accuracy of cPET-MRI registration, the first metric employed was target registration error, a commonly used measure of registration success. Because the location of a specific landmark as marked by three experts varied slightly, a "test landmark" (MR_{TEST}), defined as the centroid of the expert-defined locations for that landmark in the MR image (MR_{E1} , MR_{E2} , MR_{E3}) was created. This step was repeated for each of the 4 landmarks in each of the 17 cases. Please refer to Fig. 2 for graphical illustration of the test landmark and other concepts presented in this section. Three displacement vectors (D_{E1} , D_{E2} , D_{E3}) were determined as the vectors that relocated expert-provided locations (MR_{E1} , MR_{E2} , MR_{E3}) to match with the location of MR_{TEST} . Because MR_{E1} , MR_{E2} , MR_{E3} were sufficiently close to one another, we assumed the transformation fields to be locally linear and applied the same displacement vectors to the corresponding expert-defined locations in the PET image (PET_{E1} , PET_{E2} , PET_{E3}), generating modified landmark locations (PET_{E1}^D , PET_{E2}^D , PET_{E3}^D). The average expert-defined modified location (PET_{EXPERT}) was determined as the centroid of PET_{E1}^D , PET_{E2}^D , PET_{E3}^D , and was regarded as providing the ground truth, i.e. the location in the PET image that MR_{TEST} mapped to. The algorithm-determined transformation field (T_{ALGO}) was then used to determine a location in the PET image (PET_{ALGO}) that the test landmark (MR_{TEST}) mapped to after automatic registration. The target registration error was defined as the Euclidean distance between PET_{EXPERT} and PET_{ALGO} , averaged over all landmarks in all cases.

Because experts' views differ slightly, it is reasonable to contrast any disagreement in landmark correspondence between the algorithm and expert results with the interexpert variability as an additional accuracy metric and to judge whether the algorithm's performance is comparable to that of a typical expert [12, 16]. To this end, the 4 PET points per test landmark (1 from the algorithm and the rest provided by 3 experts) were allocated to 4 separate groups of 3 each, as illustrated in Fig. 3. The reference group consisted of the 3 experts: PET_{E1}^D , PET_{E2}^D , PET_{E3}^D . Other groups were formed by replacing one of the experts with the algorithm. For each group, the median of Euclidean distance between 3 PET point pairs within that group for all landmarks and all cases were calculated (i.e., median of $3 \times 4 \times 18$ distances). Comparable median values obtained for all 4 groups is an indication of good agreement between the algorithm-determined and the 3 expert-determined point correspondences. As in a similar registration validation study [16], a sign test, suitable for studies with small sample size, was performed to assess if the median distance for each group of groups 1–3 was equal to the median distance for the reference group. For this test, a p -value < 0.05 was used as the criterion to reject the null hypothesis and to indicate a statistically significant difference.

Results

For all 17 patients, image data were successfully retrieved from the hospital PACS (Synapse; Fujifilm Medical System, Stamford, CT, USA) into the independent registration workstation. The entire computation time, including preprocessing, initial image seeding and deformable image registration, averaged 97 ± 45 s. As shown in Fig. 4, PET and MRI provide complementary information, particularly useful in the characterization of complex oncologic processes. Figure 5 shows more examples of fused cPET-MR images after deformable registration. Following registration, as described before, a total of 64 background volumes of interest were assessed in 16 patients, and 18 neoplastic volumes of interest were assessed in 15 patients. In all, 82 volumes of interest were selected and analyzed, and the results are summarized in Table 1. Resampling the PET image during the coregistration process causes the difference in SUV_{max} between PET/CT and coregistered PET/MRI.

Of the 17 patients, each with 4 anatomical landmarks, the average target registration error was 10.7 ± 6.6 mm. The average voxel sizes (diagonal distance) were 6.1 mm for MRI and 5.8 mm for PET. Figure 5 illustrates the opportunity to perform fusion of PET data to post-contrast imaging. As shown in Fig. 6, even in structures that move significantly due to breathing, the fused cPET/MRI data set is similar in appearance to conventional PET/CT. More examples of cPET/MRI fusion are shown in Fig. 7. Table 2 summarizes the variability, in terms of pairwise distances, for the reference group and the groups containing algorithm-defined alignment. P -values of sign test between the reference group and test groups are also given. The results suggest that the algorithm's solution is not significantly different from those of the experts.

Discussion

The purpose of this study was to demonstrate and evaluate a novel software-based solution for automated deformable registration of body PET and MRI data sets as an alternative to

the dedicated hybrid PET/MRI hardware. To be clinically viable, a software system needs to meet three important criteria: 1) ease and speed of image registration, 2) PET data fidelity and 3) spatial accuracy of the coregistered images. We investigated each of these in this study.

High-speed coregistered data set creation and an ability to interface with the commercially available PACS and nuclear medicine workstations are essential for any third-party advanced application to be used clinically. Utilizing a dedicated processing workstation and advance graphical processing unit optimization, the registration algorithm implemented created a coregistered data set in approximately 1 ½ min. The registration capability is integrated into our clinical PACS in a similar way as in the study by Li et al. [17]. Time to pull and push data from PACS is based on network configuration, and the minute-order data transfer time we achieved is comparable to the transfer times between scanners, PACS servers and viewing workstations, satisfying the first criterion for the eventual clinical implementation.

A second key criterion in software-based registration is to ensure that algorithm does not impact the fidelity of the PET data, particularly SUV_{max} , given its utilization in clinical assessment. The overall absolute SUV_{max} difference was 0.27 with a relative difference of 7% for all volumes of interest ($n=82$) (Table 1). In 75 of 84 volumes of interest, cPET SUV_{max} values were lower than the corresponding PET SUV_{max} values. This is expected from the averaging of voxel intensities from data resampling after deformable registration. In the nine remaining volumes of interest, cPET SUV_{max} was higher than the respective PET SUV_{max} and was likely due to inhomogeneity of tissue uptake and slight variation in volume of interest placement. In these 9 cases, the average absolute SUV_{max} increase was 0.13, equivalent to a relative difference of 14%. Variations in SUV_{max} within the same patient between scans are known to be present depending on blood glucose levels, FDG uptake time and recent medication administration, among other factors. Test-retest reproducibility has previously shown that differences in SUV_{max} of 20% are necessary to avoid errors in interpretation due to technical variances [18]. Allowing for these known limitations, the small absolute and relative differences we observed are within system limitations and unlikely to impact clinical interpretation.

Comparing absolute and relative differences in SUV_{max} between PET/CT and cPET/MRI generated with our software to those of hybrid PET/MRI scanners is another strategy for validating PET fidelity, but such comparison is complicated because of a variety of factors. Published data on hybrid PET/MRI scanners have utilized sequential PET/CT and PET/MRI scanning to utilize a single FDG dose [19–23]. The inherent decay of ^{18}F and variable distribution of FDG uptake in normal tissues over time [24] also affects the SUV_{max} reading between successive scans. Prior studies have instead characterized the correlation value between PET/MRI and PET/CT SUV_{max} [19–22] of normal background tissues. Utilizing a Spearman's correlation coefficient, we found an excellent overall correlation value of 0.99 for all analyzed volumes of interest including both background tissue ($n=64$) and focal lesions ($n=18$). Overall correlation values, as well as subtype correlation for each tissue type, were higher than those reported previously as detailed in Table 3.

Yet another key criterion in software-based registration is accurate spatial mapping between data sets, and this accuracy usually depends on the spatial resolution of the two imaging data sets involved. When compared to hybrid PET/MRI scanner data, our overall misregistration, as measured by the target registration error, is greater than those previously reported: 2.14 ± 1.38 mm for T1-weighted and 2.24 ± 1.12 mm for T2-weighted MRI sequences [25], and 7.7 mm [26] and 5.8 ± 2.8 mm [27] for short tau inversion recovery (STIR) MRI sequences. However, these studies, in general, included higher-resolution images compared to ours. In addition to looking at hybrid PET/MRI, Schmidt et al. [26] and Brendle et al. [27] also analyzed misregistration for retrospectively fused PET and MRI data, using software-based rigid registration. In both studies, the PET image resolution was $1.78 \text{ mm} \times 1.78 \text{ mm} \times 2 \text{ mm}$, and the MR image resolution was similar to ours. The Schmidt study reported an average misregistration of 17.1 mm or approximately 5 times the average voxel size (diagonal distance), whereas the Brendle study reported an average misregistration of 11.9 ± 6.3 mm or approximately 4 times the average voxel size. In contrast, our target registration error is approximately twice the average voxel size of the PET data. These results underscore (1) the need and superiority of deformable registration over rigid registration, when the anatomy hasn't deformed rigidly, and (2) effectiveness of our deformable image registration.

In a study focusing on software-based deformable registration of PET and CT, Shekhar et al. [12] reported comparable average misregistration and interexpert variability: 5.5 mm and 5.6 mm, respectively, for data from separate scanners, and 5.9 mm and 6.6 mm, respectively, for data from a hybrid PET/CT scanner. We found a similar trend in that the average target registration error (10.7 mm) was comparable to the average interexpert variability in landmark identification (10.2 mm).

For the purposes of this study, we specifically sought to examine the feasibility of image registration for body imaging of oncological processes. Most of the anatomical landmarks included for validation were intentionally chosen to be located in the upper abdomen to test the accuracy of our coregistration algorithm in structures expected to move considerably from normal diaphragmatic excursion. Because our MRI data sets were obtained as part of a retrospective review, protocols were not standardized with voxel size variability, particularly in the z-axis. As these structures had greater z-axis motion, our observed target registration error was affected by larger voxel dimension along the z-axis. Similar findings have previously been reported by both Rakheja et al. [25] and Schmidt et al. [26], who found the largest variability in z-axis offset relative to in-plane x- and y-axis offsets.

Assessment of SUV_{max} in subcentimeter lesions is limited by scanner resolution and partial volume averaging. The target registration error we obtained is adequate to localize lesions that would be accurately characterized on PET. Further software optimization, as well as the use of data acquired via volumetric MRI acquisitions, should lower target registration error further.

Integrated PET/MRI systems offer advantages that cannot be readily achieved with software-based registration of separately acquired PET/CT and MRI data sets. These include a single sedation/anesthesia session for both PET and MRI acquisitions, patient convenience arising

from a single imaging session, and shorter overall image acquisition time. However, there are several scenarios in which our algorithm would be particularly suited. Replacing diagnostic CT with low-dose CT for purposes of attenuation correction has been reported to result in dose reductions of 50%–65% [28]. Additional work by Fahey et al. [29] using anthropomorphic phantoms demonstrated that when CT was used solely for the purposes of attenuation correction, dose reductions to 4% of diagnostic levels were achievable. In the clinical scenario in which a patient was receiving a staging or restaging body MRI, the use of our algorithm in combination with an attenuation correction only-dose PET/CT would result in decreased patient dose. Likewise, if a patient with a known malignancy, or syndrome predisposing to development of malignancy, such as neurofibromatosis, were to have a suspicious finding on conventional MRI imaging, the image registration of the MRI with PET with ultralow-dose (attenuation correction only) CT could provide data regarding the functional nature of a lesion while minimizing radiation exposure.

One situation in which our algorithm could fail is if a procedure, such as resection, takes place between the PET/CT and MR acquisitions. A general limitation of this study is retrospective analysis of previously acquired data resulting in variability of data, particularly the MRI voxel size. Efforts were made to utilize the same MRI sequence (axial post-contrast T1-weighted images), but in two cases, post-contrast images were not obtained and alternative noncontrast sequences had to be employed for registration. While this study examined single-station MRI series, the processing time for multistation body imaging would be expected to scale linearly with resultant cMRI data available to correspond to each imaging station. Given the robustness of the algorithm, multiplanar registration is a possibility in addition to multistation registration. Finally, we did not seek to address the applicability of our algorithm to head and neck or dedicated brain imaging. Given our algorithm's ability to recover soft-tissue deformations, it is ideally suited for extracranial anatomy. Therefore, this study focused on body PET/MRI fusion that warrants deformable registration

Conclusion

In the continuously evolving world of pediatric oncology, the need for accurate imaging, both functional and anatomical, is of utmost importance. Hybrid PET/MRI scanners represent the cutting edge of imaging technology, merging complementary imaging modalities to provide detailed anatomical and functional results. The cost of implementing such a program, particularly at standalone pediatric centers where PET imaging volume is a fraction of that of adult centers, makes its implementation unachievable for many facilities. The high-speed software-based solution we described is capable of providing a clinically useful and accurate imaging, and therefore achieves the benefits of hybrid PET/MRI scanners without the added financial and infrastructure investment.

Acknowledgments

This work was supported by a National Institutes of Health grant R42CA137886.

References

1. Chawla SC, Federman N, Zhang D, et al. Estimated cumulative radiation dose from PET/CT in children with malignancies: a 5-year retrospective review. *Pediatr Radiol.* 2010; 40:681–686. [PubMed: 19967534]
2. Rathore N, Eissa H, Margolin JF, et al. Pediatric Hodgkin lymphoma: Are we over-scanning our patients? *Pediatr Hematol Oncol.* 2012; 29:415–423. [PubMed: 22632168]
3. Krille L, Zeeb H, Jähnen A, et al. Computed tomographies and cancer risk in children: a literature overview of CT practices, risk estimations and an epidemiologic cohort study proposal. *Radiat Environ Biophys.* 2012; 51:103–111. [PubMed: 22310909]
4. Miglioretti D, Johnson E, Williams A, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. *JAMA Pediatr.* 2013; 167:700–707. [PubMed: 23754213]
5. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet.* 2012; 380:499–505. [PubMed: 22681860]
6. Lassman M, Treves ST. EANM/SNMMI Paediatric Dosage Harmonization Working Group. Paediatric radiopharmaceutical administration: harmonization of the 2007 EANM paediatric dosage card (version 1.5.2008) and the 2010 North American consensus guidelines. *Eur J Nucl Med Mol Imaging.* 2014; 41:1036–1041. [PubMed: 24599377]
7. Gelfand MJ, Parisi MT, Treves ST. Pediatric Nuclear Medicine Dose Reduction Workgroup. Pediatric radiopharmaceutical administered doses: 2010 North American consensus guidelines. *J Nucl Med.* 2011; 52:318–322. [PubMed: 21233182]
8. Fahey FH. Dosimetry of pediatric PET/CT. *J Nucl Med.* 2009; 50:1483–1491. [PubMed: 19690036]
9. Gelfand MJ, Lemen LC. PET/CT and SPECT/CT dosimetry in children: the challenge to the pediatric imager. *Semin Nucl Med.* 2007; 37:391–398. [PubMed: 17707244]
10. Gelfand MJ. Dosimetry of FDG PET/CT and other molecular imaging applications in pediatric patients. *Pediatr Radiol.* 2009; 39:S46–S56. [PubMed: 19083225]
11. Walimbe V, Shekhar R. Automatic elastic image registration by interpolation of 3D rotations and translations from discrete rigid-body transformations. *Med Image Anal.* 2006; 10:899–914. [PubMed: 17079184]
12. Shekhar R, Walimbe V, Shanker R. Automated 3-dimensional elastic registration of whole-body PET and CT from separate or combined scanners. *J Nucl Med.* 2005; 46:1488–1496. [PubMed: 16157532]
13. Studholme C, Hill DLG, Hawkes DJ. An overlap invariant entropy measure of 3D medical image alignment. *Pattern Recognit.* 1999; 32:71–86.
14. Mattes D, Haynor DR, Vesselle H, et al. PET-CT image registration in the chest using free-form deformations. *IEEE Trans Med Imaging.* 2003; 22:120–128. [PubMed: 12703765]
15. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the quantitative image network. *Magn Reson Imaging.* 2012; 30:1323–1341. [PubMed: 22770690]
16. Lei P, Dandekar O, Widlus D, Shekhar R. Incorporation of preprocedural PET into CT-guided radiofrequency ablation of hepatic metastases: a nonrigid image registration validation study. *J Digit Imaging.* 2010; 23:780–792. [PubMed: 19472008]
17. Li W, Robertson M, Plishker W, et al. Integration of high-speed single- and multi-modality deformable image registration with clinical PACS. *Pediatr Radiol.* 2014; 44(Suppl 1):S93–S94.
18. de Langen AJ, Vincent A, Velasquez LM, et al. Repeatability of 18F-FDG uptake measurements in tumors: a metaanalysis. *J Nucl Med.* 2012; 53:701–708. [PubMed: 22496583]
19. Heusch P, Buchbender C, Beiderwellen K, et al. Standardized uptake values for [¹⁸F] FDG in normal organ tissues: Comparison of whole-body PET/CT and PET/MRI. *Eur J Radiol.* 2013; 82:870–876. [PubMed: 23394765]
20. Kershah S, Partovi S, Traugher BJ, et al. Comparison of standardized uptake values in normal structures between PET/CT and PET/MRI in an oncology patient population. *Mol Imaging Biol.* 2013; 15:776–785. [PubMed: 23632951]

21. Pace L, Nicolai E, Luongo A, et al. Comparison of whole-body PET/CT and PET/MRI in breast cancer patients: Lesion detection and quantitation of ¹⁸F-deoxyglucose uptake in lesions and in normal organ tissues. *Eur J Radiol.* 2014; 83:289–296. [PubMed: 24331845]
22. Wiesmuller M, Quick H, Navalpakkam B, et al. Comparison of lesion detection and quantitation of tracer uptake between PET from a simultaneously acquiring whole-body PET/MR hybrid scanner and PET from PET/CT. *Eur J Nucl Med Mol Imaging.* 2013; 40:12–21. [PubMed: 23053323]
23. Drzezga A, Souvatzoglou M, Eiber M, et al. First clinical experience with integrated whole-body PET/MR: Comparison to PET/CT in patients with oncologic diagnoses. *J Nucl Med.* 2012; 53:845–855. [PubMed: 22534830]
24. Chin BB, Green ED, Turkington TG, et al. Increasing uptake time in FDG-PET: Standardized uptake values in normal tissues at 1 versus 3 h. *Mol Imaging Biol.* 2009; 11:118–122. [PubMed: 19037614]
25. Rakheja R, DeMello L, Chandarana H, et al. Comparison of the accuracy of PET/CT and PET/MRI spatial registration of multiple metastatic lesions. *AJR Am J Roentgenol.* 2013; 201:1120–1123. [PubMed: 24147486]
26. Schmidt H, Brendle C, Schraml C, et al. Correlation of simultaneously acquired diffusion-weighted imaging and 2-deoxy-[¹⁸F] fluoro-2-D-glucose positron emission tomography of pulmonary lesions in a dedicated whole-body magnetic resonance/positron emission tomography system. *Invest Radiol.* 2013; 48:247–255. [PubMed: 23519008]
27. Brendle CB, Schmidt H, Fleischer S, et al. Simultaneously acquired MR/PET images compared with sequential MR/PET and PET/CT: alignment quality. *Radiology.* 2013; 268:190–199. [PubMed: 23657890]
28. Gelfand MJ, Lemen LC. PET/CT and SPECT/CT dosimetry in children: the challenge to the pediatric imager. *Semin Nucl Med.* 2007; 37:391–398. [PubMed: 17707244]
29. Fahey FH, Palmer MR, Strauss KJ, et al. Dosimetry and adequacy of CT-based attenuation correction for pediatric PET: phantom study. *Radiology.* 2007; 243:96–104. [PubMed: 17293575]

Fig. 1.
Pictorial representation of volume subdivision algorithm used with the graphical processing unit-accelerated registration

Fig. 2.

Graphical illustration of calculating the target registration error. MR_{E1} , MR_{E2} , MR_{E3} , PET_{E1} , PET_{E2} , PET_{E3} denote the expert-defined landmarks. MR_{TEST} is the average of MR_{E1} , MR_{E2} , MR_{E3} . D_{E1} , D_{E2} , D_{E3} denote displacement vectors. PET_{E1}^D , PET_{E2}^D , PET_{E3}^D denote PET_{E1} , PET_{E2} , PET_{E3} after applying displacement vectors. PET_{EXPERT} is the average of PET_{E1}^D , PET_{E2}^D , PET_{E3}^D . T_{ALGO} is the algorithm-determined transformation. PET_{ALGO} is the software-mapped MR_{TEST} .

Fig. 3. Graphical illustration of pairwise differences for the evaluation of interexpert variability. **a** Reference group with all three expert-defined PET points (PET_{E1}^D , PET_{E2}^D , PET_{E3}^D). **b–d** Groups 1–3 include the algorithm-defined PET point (PET_{ALGO}) and two expert-defined PET points

Fig. 4. MRI offers considerable improvement in the visualization of hepatoblastoma in a 27-month-old girl. PET imaging better demonstrates the heterogeneity of lesion with large areas of viable tumor, and areas of relative photopenia suggesting necrosis. The coregistered PET/MR image using our software-based solution is shown on the top-right panel

Fig. 5. The complementary nature of PET and MRI is emphasized by areas of absent PET uptake in previously treated posterior right hepatic lobe metastasis and avidity of untreated anterior right and left hepatic lobe metastasis in an 11-year-old girl with rhabdomyosarcoma. **a** Post-contrast MRI. **b** cPET/MRI

Fig. 6. Comparison of PET/CT (**a**) and cPET/MRI (**b**) of a 12-year-old boy with lymphoma and thoracic lymphadenopathy. Note the registration is visually acceptable even when motion artifacts are present in the MR images

Fig. 7.

More examples of cPET/MRI fusion in (a) a 12-year-old boy with lymphoma involving subcarnial lymph nodes, (b) an 11-year-old girl with hepatocellular carcinoma and (c) a 6-month-old boy with metastatic primitive neuroectodermal tumor involving the right ischium and inferior pubic ramus

Table 1

Standardized uptake value (SUV) results based on volumes of interest

Location (#)	PET/CT SUV _{max} Mean [Range]	cPET/MRI SUV _{max}	Absolute Difference	Relative Difference ^a	P [*]
Lung (11)	0.7 [0.5–1.1]	0.7 [0.4–1.3]	0.06 [0–0.2]	9% [0–25%]	0.90
Liver (11)	1.8 [1.2–2.4]	1.8 [1.2–2.4]	0.64 [0–0.2]	4% [0–12%]	0.96
Kidney (10)	9.5 [4.3–15.8]	8.7 [4.2–14.7]	0.79 [0.1–2.2]	8% [2–17%]	0.99
Muscle (16)	0.8 [0.6–1.5]	0.8 [0.5–1.4]	0.08 [0–0.3]	9% [0–30%]	0.73
Bone (16)	2.7 [1–11.6]	2.6 [0.9–11.1]	0.13 [0–0.5]	6% [0–23%]	0.99
Lesions (18)	7.2 [1.4–26.3]	6.6 [1.3–24.9]	0.52 [0–2]	8% [0–27%]	0.99
Overall (82)	3.8 [0.5–26.3]	3.5 [0.4–24.9]	0.27 [0–2]	7% [0–30%]	0.99

^aRelative difference, (PET/CT SUV_{max} – cPET/MRI SUV_{max})/(PET/CT SUV_{max})^{*}Spearman's rank correlation coefficient between PET/CT SUV_{max} and cPET/MRI SUV_{max}

cPET coregistered PET, PET positron emission tomography

Table 2

Interexpert/algorithm variability in landmark alignment between MR and PET images

Median pair-wise difference of all anatomical landmarks for all patients (mm) [IQR [*]] (<i>p</i> -value [#])			
Reference group	Group 1	Group 2	Group 3
9.8 [9.1]	10.7 [12.1] (0.06)	10.3 [8.9] (0.08)	10.0 [8.5] (0.44)

^{*} Interquartile range[#] *p*-value calculated from sign test between the reference group and a test group

Comparison of Spearman's correlation coefficient of SUV_{max} for cPET/MRI and PET/CT with that from published studies on PET/MRI and PET/CT

Table 3

	Lung	Liver	Kidney	Muscle	Bone	Lesions	Overall
Our registration algorithm	0.926	0.968	0.988	0.776	0.991	0.995	0.993
Heusch 2013 [19]	---	0.65	---	---	0.42	---	---
Kershah 2013 [20]	0.70	0.68	---	0.41	0.80	---	---
Pace 2014 [21]	0.48	0.36	---	0.38	---	0.71	---
Wiesmuller 2013 [22]	---	---	---	---	---	---	0.71

cPET coregistered PET, PET positron emission tomography, SUV_{max} maximum standardized uptake value